REMARKS

Amendments to the Claims

Claims 1-6 and 8-20 were pending.

Claims 11-19 have been withdrawn.

Claims 1 and 20 have been amended to recite "wherein said formulation comprises one or more antitumor agents selected from the group consisting of bleomycin hydrochloride, bleomycin, bleomycin sulfate, etoposide, interferon, carboplatin, nedaplatin, nimustine hydrochloride, carboquone, melphalan, ifosfamide, thiotepa, vinorelbine, neocarzinostatin, tegafur, goserelin acetate, sobuzoxane, tretinoin, estramustine sodium phosphate, toremifene citrate, hydroxycarbamide, cytarabine ocfosfate, doxifluridine, gefinitib, imatinib mesilate, oxaliplatin, uracil-tegafur (UFT), carmofur, aceglatone, anastrozole, ubenimex, fadrozole hydrochloride hydrate, and bicalutamide." Claims 1 and 20 find support from canceled Claim 4.

Claims 1 and 20 have amended to recite "gastric and intestinal absorption."

No new matter has been added. Entry these amendments is respectfully requested.

Disposition of Claims 11-19

In the Office Action, Claims 11-19 have been indicated as withdrawn from consideration. The Examiner stated that the process set forth in Claims 11-19 are related to the product described in Claims 1-6, 8-10 and 20. Applicants request that withdrawn Claims 11-19 be considered for rejoinder when the product Claims 1-6, 8-10 and 20 are found to be allowable.

Further, the Examiner stated that: "In the instant case the method of reducing the toxicity of an antitumor agent can be performed with the antitumor agent in a sustained release porous particulate preparation not comprising hydroxyapatite" (Office Action at page 2, second paragraph; emphasis added). Applicants respectfully note that the method as in Claim 11 requires hydroxyapatite to be present in the formulation by reciting "preparing a formulation containing said antitumor agent blended with said hydroxyapatite particles." (Emphasis added). Applicants believe that the statement in the Office Action was made in error and respectfully request clarification of the statement.

Rejection of Claims 1-6, 8-10 and 20 Under 35 U.S.C. § 102(b)

Claims 1-6, 8-10 and 20 have been rejected as being anticipated by Aoki *et al.* (Aoki *et al.*, *Transactions of the Materials Research Society of Japan*, 15A: 3-9 (1994); Reference of record "C1"; hereinafter, "Aoki").

Aoki discloses absorption of doxorubincin, mitomycin C and fluorouracil in hydroxyapatite.

As noted above, Claims 3 and 4 have been canceled without prejudice, rendering the rejection moot against these claims. While Applicants maintain the arguments set forth in the previous response, in the interest of furthering prosecution, Applicants have now amended independent Claims 1 and 20 to recite specific antitumor agents as noted above. Since none of the agents recited in Claims 1 and 20, as amended, is taught by Aoki, Applicants respectfully submit that the present amendment overcomes the rejection.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-6, 8-10 and 20 Under 35 U.S.C. § 102(b)

Claims 1-6, 8-10 and 20 have been rejected as being anticipated by Lee *et al.* (WO 02/41844; Reference of record "B1"; hereinafter, "Lee"). The Examiner stated that: "Lee *et al.* discloses composition of nanocrystalline calcium phosphate paste with anti-cancer agents thus anticipating instant claims 1-4" (the Office Action at page 8).

As noted above, Claims 3 and 4 have been canceled without prejudice, rendering the rejection moot against these claims. While Applicants maintain the arguments set forth in the previous response, in the interest of furthering prosecution, Applicants have amended independent Claims 1 and 20 to recite specific antitumor agents as noted above. Further, Applicants have also amended the independent Claims 1 and 20 to recite "gastric and intestinal absorption." This amendment further distinguishes the present invention from the teachings of Lee directed to "cement" or "paste" that sets into a product upon mixing with an antitumor agent prior to intravenous injection. Because Lee does not disclose any anti-tumor agent or oral formulation recited in Claims 1 and 20, as amended, Applicants respectfully submit that the present amendments overcome the rejection.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-6, 8-10 and 20 Under 35 U.S.C. § 103(a)

Claims 1-6, 8-10 and 20 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lee. The Office Action stated that: "The difference between the instant application and Lee et al. that Lee et al. do not expressly teach all of the antitumor agents in instant claims 3 and 4. This deficiency in Lee et al. is cured by common sense" (the Office Action at page 11). Applicants disagree.

Lee discloses drug delivery vehicles containing an anticancer agent and various types of *calcium phosphates*.

However, Lee does not teach or suggest the use of hydroxyapatite (HA) particles in reducing toxicity of the antitumor agents recited in independent Claims 1 and 20, as amended. In Examples 5 an 6, Lee merely shows the effects of cisplatin loaded onto a mixture of nonchrystalline calcium phosphate (NCP) and dicalcium phosphate dihydrate (DCPD) (50%:50% by weight) on growth of a breast tumor and a prostate tumor (*see* Lee, Figs. 1 and 3). However, neither NCP nor DCPD used by Lee is hydroxyapatite. The chemical composition and physiological property (*e.g.*, biodegradability) of calcium phosphate ($Ca_3(PO_4)_2$) and its derivatives, such as dicalcium phosphate dihydrate (DCPD), are largely different from those of hydroxyapatite. In comparison, the present application is directed in reducing toxicity of the antitumor agents recited in Claims 1 and 20 by blending the anti-tumor agents with hydroxyapatite particles having a maximum size of 5 μm (*see* the Specification at page 7, lines 33-36).

Absent specific knowledge on the desirable and surprising properties of pulverized HA having a specific particle size in reducing toxicity of a specific anti-tumor agent, one of ordinary skill in the art would not have been motivated to modify the teachings of Lee to arrive at the claimed invention. Further, without having empirical data showing that pulverized HA having a specific particle size is effective in reducing toxicity of specific anti-tumor agents, the deficiencies in Lee would not be cured by common sense.

Moreover, the claimed invention achieves unexpected results which would overcome any *prima facie* case of obviousness. The present Specification states that:

> "...tests using other calcium phosphates were performed, and a slight reduction of toxicity in pulverized, tricalcium phosphate-supplemented sobuzoxane antitumor agents was observed.

> However, the reduction was not as great as that observed with pulverized hydroxyapatite-supplemented sobuzoxane antitumor agent" (the Specification at page 35, lines 2-5; emaphasis added).

Applicants also note that, throughout the Specification, calcium triphosphate was employed as a negative control that does not exert significant effects on reducing toxicity of antitumor agents (*see* the Specification at page 7, lines 33-36). Thus, the claimed invention achieves unexpected results by showing that HA particles having a maximum size of 5 μm possess unexpected superior qualities in reducing toxicity of the antitumor agents recited in Claims 1 and 20, as amended. Accordingly, even assuming, *arguendo*, that a *prima facie* case of obviousness has been established, the claimed invention effectively overcomes such obviousness.

For at least the reasons above, Lee does not render obvious Claims 1 and 20, as amended, and other claims that depends from Claim 1. Reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting Rejection

Claims 1-6, 8-10 and 20 have been provisionally rejected as being unpatentable on the ground of non-statutory obviousness-type double patenting over Claims 1-8 and 11 of copending Application No. 11/887,710 (hereinafter, "the '710 application").

In the present application, Claims 3 and 4 have been canceled, rendering the rejection moot against these claims. Independent Claims 1 and 20 have been amended as discussed above and the claims, as amended.

To expedite prosecution, however, Applicants will consider filing a terminal disclaimer to obviate any "obviousness-type" double patenting rejection, if appropriate, upon notice of allowable subject matter in either application.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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